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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/992,845	11/14/2001	Karen A. McDonald	023070-114510US	7257
20350	7590	02/18/2004		
TOWNSEND AND TOWNSEND AND CREW, LLP TWO EMBARCADERO CENTER EIGHTH FLOOR SAN FRANCISCO, CA 94111-3834			EXAMINER KALLIS, RUSSELL	
			ART UNIT	PAPER NUMBER
			1638	

DATE MAILED: 02/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/992,845	Applicant(s) MCDONALD ET AL.	
	Examiner Russell Kallis	Art Unit 1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 03 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-17 is/are pending in the application.
- 4a) Of the above claim(s) 7-13 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-6, 14-17 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 14 November 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date <u>5/30/02, 4/14/03</u> | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-6 and 14-17 in Paper No. 11/03/2003 is acknowledged. The traversal is on the ground(s) that the search for one group would pertain to the search for the other. This is not found persuasive because the method of semi-continuous culturing of untransformed rice cells monitoring for an expression product of Group I, and the semi-continuous culturing of transformed rice cells comprising a heterologous expression cassette and monitoring for a recombinant expression product of Group II have different starting materials, different method steps and different end products that would require different searches. Applicant asserts that Claim 1 is a linking claim for Groups I and II. The Examiner acknowledges this oversight in the restriction.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-17 are pending. Claims 7-13 are withdrawn. Claims 1-6 and 14-17 are examined.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6 and 14-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of semi-continuous growth of rice suspension cells transformed with the *Ramy3D* promoter operably linked to a human α_1 -antitrypsin, does not reasonably provide enablement for a method of semi-continuous growth of any plant cell

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suspension culture expressing any protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

The claimed invention is not supported by an enabling disclosure taking into account the *Wands* factors. *In re Wands*, 858/F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). *In re Wands* lists a number of factors for determining whether or not undue experimentation would be required by one skilled in the art to make and/or use the invention. These factors are: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples of the invention, the state of the prior art, the predictability or unpredictability of the art, and the breadth of the claim.

Applicant broadly claims a method for semi-continuous growth of any culture of plant cells expressing any expression product under control of any inducible promoter, comprising monitoring medium pH or the rate of oxygen uptake and exchanging the medium when the pH is above 6.5 or exchanging the medium when oxygen uptake rate is above 2.0 mmol O₂/Lhr, wherein the heterologous expression product is encoded by a human α_1 -antitrypsin gene and the plant cells are rice.

Applicant teaches semi-continuous growth of a culture of rice suspension cells optimized for expression of human α_1 -antitrypsin was sustained for three cycles of growth, producing 40, 110 and 80 mg/L of active recombinant human α_1 -antitrypsin and was induced using the *Ramy3D* promoter (pages 25- 26 specification).

Applicant does not teach a method of semi-continuous growth of any other plant suspension culture expressing any other protein or product other than rice suspension cells expressing human α_1 -antitrypsin using the inducible *Ramy3D* promoter.

The state-of-the-art is such that one of skill in the art cannot predict which culturing conditions applied to any particular species or particular cell line of plant suspension culture would result in recovery of a particular expression product. *Taxus* suspension cultures have been observed to vary with respect to optimal conditions for growth (Bringi V. *et al.*, U.S. Patent 5,407,816 issued April 18, 1995; column 6, see Suspension Growth). The unpredictability lies within the cell line or species of cell that would require unique conditions for cellular growth known to vary with cell type and the ionic nature of the expression product that when secreted into the culture would exert an influence upon the pH of the culture.

Although one of skill in the art can readily make and grow suspension cultures one would not know based upon Applicant's disclosure which embodiments would be operable, and thus undue trial and error experimentation would be needed by one skilled in the art to make and clone a multitude of gene expression constructs and would require one of skill in the art to test in a myriad of non-exemplified plant cell suspension cultures for inducible semi-continuous cell culture growth and product expression in a multitude of non-exemplified species or cell lines of transformed plant cell suspension cultures.

Given the unpredictability in the art as to which conditions for cell suspension growth in any particular plant cell suspension culture would allow for any yield of any expression product; the breadth of the claims encompassing any plant cell suspension expressing any expression product under the control of any inducible promoter; the lack of guidance in the examples of the

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specification or in the prior art as to which suspension culture growth conditions would best serve the invention; and the undue trial and error experimentation required to practice the invention, the invention is not enabled for the scope set forth in the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-6 and 14-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Terashima M. *et al.* (Appl. Microbiol. Biotechnol., 1999; Vol. 52 pages 516-523) in view of Fischer U. *et al.* (Plant Cell, Tissue and Organ Culture, 1994, Vol. 38; pages 123-134) and Applicant's admission.

Applicant broadly claims a method for semi-continuous growth of any culture of plant cells expressing any expression product under control of any inducible promoter, comprising monitoring medium pH or the rate of oxygen uptake and exchanging the medium when the pH is above 6.5 or exchanging the medium when oxygen uptake rate is above 2.0 mmol O₂/Lhr, wherein the heterologous expression product is encoded by a human α_1 -antitrypsin gene and the plant cells are rice.

Terashima teaches a method of continuous culturing of rice suspension cells transformed with a heterologous construct expressing a human α_1 -antitrypsin induced using the *Ramy3D* promoter (see Abstract).

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Terashima does not teach a method of semi-continuous culturing of rice suspension cells comprising monitoring medium pH or the rate of oxygen uptake and exchanging the medium when the pH is above 6.5 or exchanging the medium when oxygen uptake rate is above 2.0 mmol O₂/Lhr.

Fischer teaches a method of semi-continuous production of photoautotrophic cultures of *Chenopodium rubrum* (see Abstract) and Applicant admits that the pH value for optimal production will vary with the culture conditions, the type of cells, and the protein produced (see specification page 5, lines 7-11).

It would have been obvious at the time of Applicant's invention to modify the invention of Terashima to substitute a method of semi-continuous culturing as taught by Fischer for continuous culturing of transformed plant cell cultures. One of skill in the art would have been motivated by the success of Fischer that semi-continuous culturing is considered an advantage for product recovery and in semi-continuous expression of recombinant protein in semi-continuous culture, and that one would have had a reasonable expectation of success of expressing human α_1 -antitrypsin in transformed rice cell suspension cultures, considering that the optimization of protein expression by measuring the pH level in the medium for the optimal time of medium exchange or optimizing the rate of oxygen consumption to find the levels of those variables that are correlated with optimal protein expression is recognized by one of skill in the art.

All claims are rejected.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Kallis whose telephone number is (571) 272-0798. The examiner can normally be reached on M-F 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Russell Kallis Ph.D.
February 4, 2004



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